

Temporary Compliance Waiver Notice

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Initial REMS approval: 02/2013

Most recent modification: 244237

**Buprenorphine-containing Transmucosal products for Opioid Dependence
(BTOD)
Risk Evaluation and Mitigation Strategy (REMS)**

This REMS applies to buprenorphine-containing oral transmucosal products indicated for the treatment of opioid dependence (hereinafter, “buprenorphine-containing products”). This REMS does not apply to buprenorphine-containing products that are dispensed to patients admitted to an Opioid Treatment Program under 42 CFR Part 8.

I. Goals:

The goals of the Buprenorphine-containing Transmucosal products for Opioid Dependence (BTOD) REMS are to:

- Mitigate the risks of accidental overdose, misuse, and abuse
- Inform prescribers, pharmacists, and patients of the serious risks associated with buprenorphine-containing products

II. REMS ELEMENTS:

A. Medication Guide

A Medication Guide for Trade name (MG) will be dispensed with each prescription for a buprenorphine-containing product in accordance with 21 CFR 208.24.

The Medication Guides for buprenorphine-containing products are part of the BTOD REMS and will be available through the [BTOD REMS website](http://www.btodrems.com) (www.btodrems.com).

B. Elements to Assure Safe Use

1. Safe use conditions

- a. Buprenorphine-containing products will only be dispensed by the prescriber or prescribed to patients with documentation of the following safe use conditions:
 - i. Verification that the patient meets the diagnostic criteria for opioid dependence.
 - ii. Risks described in the professional labeling and the Medication Guide have been discussed with the patient.
 - iii. Safe storage of the medication has been explained and reviewed with the patient.
 - iv. After appropriate induction, the patient is prescribed a limited amount of medication at the first visit.
- b. Prescribers will document safe use conditions for each patient by using the ‘[Appropriate Use Checklist](#),’ or by using another method (e.g. electronic health record) specific to the prescriber’s office practice.
- c. Sponsors of this waiver-granted shared REMS (BTOD Sponsors) will ensure that within 60 days of FDA approval of the BTOD REMS, a [Dear Prescriber Letter](#) will be mailed to all prescribers certified to treat opioid dependence under the Drug Addiction Treatment Act of 2000 (DATA 2000). This letter is designed to convey and reinforce the risks of accidental overdose, misuse, and abuse of buprenorphine-containing products, as well as the need to appropriately monitor patients and document safe use conditions. The prescriber brochure, [Office-Based Buprenorphine Therapy for Opioid Dependence: Important Information for Prescribers](#), and the [Appropriate Use Checklist](#) will be appended to the [Dear Prescriber Letter](#). The letter will provide instructions on where to obtain copies of the Full Prescribing Information and Medication Guides. Mailings will occur annually thereafter.

- d. BTOD Sponsors will, on a monthly basis, identify any newly DATA 2000-certified prescribers and mail the applicable documents to them. The prescriber brochure, *Office-Based Buprenorphine Therapy for Opioid Dependence: Important Information for Prescribers* and the *Appropriate Use Checklist* will be appended to the *Dear Prescriber Letter*. The letter will provide instructions on where to obtain copies of the Full Prescribing Information and Medication Guides.
- e. To further reinforce safe use conditions, BTOD Sponsors will ensure that within 60 days of FDA approval of the BTOD REMS, a *Dear Pharmacist Letter* will be mailed to all retail pharmacies authorized by DEA to handle schedule III controlled substances on a national mailing list from the National Technical Information Service. The pharmacist brochure, *Office-Based Buprenorphine Therapy for Opioid Dependence: Important Information for Pharmacists* will be appended to the *Dear Pharmacist Letter*. The letter will provide instructions on where to obtain copies of the Full Prescribing Information and Medication Guides. Mailings will occur annually thereafter.
- f. BTOD Sponsors will make the letters and all materials that are appended to the letters available through its toll-free information line, through BTOD REMS specialists and on the *BTOD REMS website*.
- g. On a monthly basis, the BTOD REMS specialists will make attempts to contact all newly certified prescribers listed on the SAMHSA website and a random sample of existing prescribers via outbound call center calls.
 - 1. The BTOD REMS specialists will create awareness of the program, confirm that REMS materials have been received by the prescriber, and confirm understanding of the BTOD REMS requirements.
 - 2. The BTOD REMS specialists will mail a copy of the REMS materials to prescribers who did not receive or request the REMS materials.
 - 3. The BTOD REMS specialists will offer to provide additional follow-up information. If further follow-up is requested, the BTOD REMS specialist will offer the following options:
 - Option I: A BTOD REMS specialist will provide a live online meeting to review BTOD REMS requirements
 - Option II: A BTOD REMS specialist will provide a field visit to review BTOD REMS requirements

2. Monitoring

- a. Each patient using a buprenorphine-containing product will be subject to the following monitoring:
 - i. Return visits are scheduled at intervals commensurate with patient stability. Weekly, or more frequent, visits are recommended for the first month.
 - ii. Assessment and reinforcement of patient's compliance with the prescribed medication.
 - iii. Assessment of appropriateness of dosage prescribed.

- iv. Assessment of whether patient is receiving the necessary psychosocial support.
- v. Assessment of whether patient is making adequate progress towards treatment goals.
- b. Prescribers will document that each patient has received the required clinical monitoring using the ‘[Appropriate Use Checklist](#),’ or by using another method/system (e.g. electronic health record) specific to the prescriber’s office practice.

The following materials are part of the BTOD REMS and are appended to the REMS document:

- [Dear Prescriber Letter](#)
- [Dear Pharmacist Letter](#)
- [Appropriate Use Checklist](#)
- Prescriber Brochure, “*Office-Based Buprenorphine Therapy for Opioid Dependence: Important Information for Prescribers*”
- Pharmacist Brochure, “*Office-Based Buprenorphine Therapy for Opioid Dependence: Important Information for Pharmacists*”
- [BTOD REMS Website \(www.btodrems.com\)](#)

C. Implementation System

BTOD Sponsors will:

- Ensure that all DATA 2000-certified prescribers receive the [Dear Prescriber Letter](#) with the appended materials.
- Monitor compliance with the prescriber requirements to document prescribing and dispensing with documentation of safe use conditions through surveys of patients and prescribers, evaluations of health care utilization databases, and ongoing surveillance (sources including, but not limited to, internet, national databases, and surveys conducted at substance abuse treatment programs).
- Monitor and evaluate the implementation of the elements to assure safe use provided for under [Sections B1](#), above, and in the manner described in the REMS supporting document, and take reasonable steps to improve implementation of these elements to meet the goals of the BTOD REMS, if the goals of the REMS are not being met.

D. Timetable for Submission of Assessments

The BTOD submission of assessments occurs annually with a due date of August 30th, beginning in 2014. To facilitate inclusion of as much information as possible, while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment will conclude no earlier than 60 days before the submission date for that assessment. The NDA holder(s) will submit each assessment so that it will be received by the FDA on or before the due date.



IMPORTANT DRUG WARNING

Subject: Risk Evaluation and Mitigation Strategy (REMS) for buprenorphine-containing transmucosal products for opioid dependence due to their risks of accidental overdose, misuse, and abuse.

Dear Prescriber:

You are receiving this letter because you are a prescriber certified to treat opioid dependence under the Drug Addiction Treatment Act of 2000 (DATA 2000).

The purpose of this letter is to inform you of a Risk Evaluation and Mitigation Strategy (REMS) called the Buprenorphine-containing Transmucosal products for Opioid Dependence (BTOD) REMS program. This REMS does not apply to buprenorphine-containing products that are dispensed to patients in an Opioid Treatment Program (OTP) under 42 CFR Part 8.

The FDA has determined that a REMS is necessary to ensure that the benefits of buprenorphine-containing transmucosal products for opioid dependence outweigh the potential risks of accidental overdose, misuse, and abuse. Products containing the single active ingredient buprenorphine are indicated for the treatment of opioid dependence and are preferred for induction. Products containing buprenorphine with naloxone are indicated for the maintenance treatment of opioid dependence. These products are used as part of a complete treatment plan, including counseling and psychosocial support.

Serious Risks of Buprenorphine-containing Products

The following key messages need to be communicated to patients about the risks of accidental overdose, misuse, and abuse while taking products covered under the BTOD REMS program:

- Warn patients that it is extremely dangerous to self-administer non-prescribed benzodiazepines or other central nervous system (CNS) depressants (including alcohol) while taking these products. Caution patients prescribed benzodiazepines or other CNS depressants to use them only as directed by their prescriber.
- Instruct patients to keep these products in a secure place, out of the sight and reach of children. Accidental or deliberate ingestion by a child may cause respiratory depression that can result in death. If a child is exposed to one of these products, medical attention should be sought immediately.
- Advise patients that these products contain an opioid that can be a target for people who abuse prescription medications or street drugs. Caution patients to keep their products in a safe place, and to protect them from theft.
- Instruct patients never to give these products to anyone else, even if he or she has the same signs and symptoms. It may cause harm or death.
- Advise patients that selling or giving away these products is against the law.

Prescriber Action

Certified prescribers must read the enclosed educational brochure entitled *Office-Based Buprenorphine Therapy for Opioid Dependence: Important Information for Prescribers*. Under the BTOD REMS program, prescribers are strongly encouraged to perform and document all of the following actions:

- Verify the patient meets diagnostic criteria for opioid dependence
- Discuss the risks associated with buprenorphine-containing products, including those described in the Medication Guide
- Provide induction doses under appropriate supervision
- Prescribe a limited amount of medication to the patient that will last until the next visit
- Explain how to safely store the medication out of reach of children
- Schedule patient appointments commensurate with patient stability (weekly or more frequent visits recommended for the first month)

- Consider “pill count”/dose reconciliation
- Assess whether the patient is receiving the counseling/psychosocial support considered necessary for treatment
- Assess whether the patient is making progress toward treatment goals, including, as appropriate, urine toxicology testing
- Continually assess appropriateness of maintenance dose
- Continually assess benefits of treatment outweigh the risks

Patient Monitoring and Appropriate Dosing Info

An [Appropriate Use Checklist](#) is enclosed to assist you in performing and documenting the above prescriber actions of the BTOD REMS. You may use the enclosed checklist or other means (e.g. electronic health record) specific to your office practice to document that the above actions have been completed for each patient.

Medication Guide

The BTOD REMS includes product specific Medication Guides with important information to be reviewed with patients. In addition, the Medication Guide will be dispensed with each prescription for a buprenorphine-containing transmucosal product.

Reporting Adverse Events

To report SUSPECTED ADVERSE EVENTS contact:

- The manufacturer of the product taken or
- FDA MedWatch program by phone at 1-800-FDA-1088 or online at www.fda.gov/medwatch/report.htm

This letter is not a comprehensive description of the risks associated with the use of buprenorphine-containing transmucosal products. Additional important safety information can be found in the [Office-Based Buprenorphine Therapy for Opioid Dependence: Important Information for Prescribers](#) educational brochure and Full Prescribing Information.

Additional copies of the educational brochure, [Appropriate Use Checklist](#), Full Prescribing Information, and Medication Guide for each product covered under the BTOD REMS, can be obtained at www.btodrems.com or by contacting the toll-free call center at 1-855-223-3922.

Sincerely,

The Buprenorphine-containing Transmucosal products
for Opioid Dependence Companies

Version 1.0 Revised February 2013

Enclosures: [Appropriate Use Checklist](#)
[Office-Based Buprenorphine Therapy for Opioid Dependence:
Important Information for Prescribers](#)



IMPORTANT SAFETY INFORMATION

Subject: Risk Evaluation and Mitigation Strategy (REMS) for buprenorphine-containing transmucosal products for opioid dependence due to their risks of accidental overdose, misuse, and abuse.

<DATE>

Dear Pharmacist:

The purpose of this letter is to inform you of a Risk Evaluation and Mitigation Strategy (REMS) called the Buprenorphine-containing Transmucosal products for Opioid Dependence (BTOD) REMS program. This REMS does not apply to buprenorphine-containing products that are dispensed to patients in an Opioid Treatment Program (OTP) under 42 CFR Part 8.

The FDA has determined that a REMS is necessary to ensure that the benefits of buprenorphine-containing transmucosal products for opioid dependence outweigh the potential risks of accidental overdose, misuse, and abuse. Products containing the single active ingredient buprenorphine are indicated for the treatment of opioid dependence and are preferred for induction. Products containing buprenorphine with naloxone are indicated for the maintenance treatment of opioid dependence. These products are used as part of a complete treatment plan, including counseling and psychosocial support.

Serious Risks of Buprenorphine-containing Products

The following key messages need to be communicated to patients about the risks of accidental overdose, misuse, and abuse while taking products covered under the BTOD REMS program:

- Warn patients that it is extremely dangerous to self-administer non-prescribed benzodiazepines or other central nervous system (CNS) depressants (including alcohol) while taking buprenorphine-containing products. Patients prescribed benzodiazepines or other CNS depressants should be cautioned to use them only as directed by their prescriber
- Instruct patients to keep buprenorphine-containing products in a secure place, out of the sight and reach of children. Accidental or deliberate ingestion by a child may cause respiratory depression that can result in death. Patients should be advised that if a child is exposed to buprenorphine-containing products, medical attention should be sought immediately
- Advise patients that buprenorphine-containing products contain an opioid that can be a target for people who abuse prescription medications or street drugs. Patients should be cautioned to keep their products in a safe place, and to protect them from theft
- Instruct patients never to give buprenorphine-containing products to anyone else, even if he or she has the same signs and symptoms. It may cause harm or death
- Advise patients that selling or giving away this medication is against the law

Pharmacist Action

Pharmacists are encouraged to read the enclosed educational brochure entitled *Office-Based Buprenorphine Therapy for Opioid Dependence: Important Information for Pharmacists*. Each time you fill a prescription for a buprenorphine-containing product, make sure to:

- Verify that the prescription you receive is from a prescriber who is in compliance with the provisions of DATA 2000
- Keep in mind that a limited supply of buprenorphine-containing products should be dispensed during the initiation of therapy. This is due to the need of prescribers to closely and frequently assess the patients' needs, their symptoms, and potential risk of misuse, diversion, and abuse
- Provide the Medication Guide to patients each time the medicine is dispensed

- Remind patients who are picking up induction doses to return as directed to the doctor's office so that they can be supervised while taking the medication
- Provide appropriate patient counseling on safe use of buprenorphine-containing products
- Be vigilant in detecting fraudulent prescriptions or simultaneous prescriptions for the same patient from multiple prescribers

Medication Guide

The BTOD REMS includes product specific Medication Guides on the safe and effective use of buprenorphine-containing products, and the importance of participating in psychosocial support with important information to be reviewed with patients. It is important that you provide a Medication Guide to your patients or their caregivers with each dispensing and encourage them to read it.

Reporting Adverse Events

To report SUSPECTED ADVERSE EVENTS contact:

- The manufacturer of the product taken or
- FDA MedWatch program by phone at 1-800-FDA-1088 or online at www.fda.gov/medwatch/report.htm

This letter is not a comprehensive description of the risks associated with the use of buprenorphine-containing transmucosal products. Additional important safety information can be found in the [Office-Based Buprenorphine Therapy for Opioid Dependence: Important Information for Pharmacists](#) educational brochure and Full Prescribing Information.

Additional copies of the educational brochure, Full Prescribing Information, and Medication Guide for each product covered under the BTOD REMS, can be obtained at www.btodrems.com or by contacting the toll-free call center at 1-855-223-3922.

Sincerely,

The Buprenorphine-containing Transmucosal products
for Opioid Dependence Companies

Version 1.0 Revised February 2013

Enclosures: [Office-Based Buprenorphine Therapy for Opioid Dependence:
Important Information for Pharmacists](#)



Patient Name: _____

APPROPRIATE USE CHECKLIST: BUPRENORPHINE-CONTAINING TRANSMUCOSAL PRODUCTS FOR OPIOID DEPENDENCE

This checklist is a useful reminder of the safe use conditions and monitoring requirements for prescribing buprenorphine-containing transmucosal products for opioid dependence.

Requirements to address during each patient's appointment include:

- understanding and reinforcement of safe use conditions
- the importance of psychosocial counseling
- screening and monitoring patients to determine progress towards treatment goals

If a patient continues to abuse various drugs or is unresponsive to treatment, including psychosocial intervention, it is important that you assess the need to refer the patient to a specialist and/or a more intensive behavioral treatment environment.

Additional resource: Physician Clinical Support System: <http://pcssb.org/>

This checklist may be used during the induction period and filed in patient's medical record to document safe use conditions. Once a maintenance dose has been established, use the maintenance checklist.

MEASUREMENT TO ENSURE APPROPRIATE USE	NOTES
Date:	
INDUCTION	
<input type="checkbox"/> Verified patient meets diagnostic criteria for opioid dependence	
<input type="checkbox"/> Discussed risks described in professional labeling and Medication Guide with patient	
<input type="checkbox"/> Explained or reviewed conditions of safe storage of medication	
<input type="checkbox"/> Provided induction doses under appropriate supervision	
<input type="checkbox"/> Prescribed limited amount of medication at first visit	
<input type="checkbox"/> Scheduled next visit at interval commensurate with patient stability <ul style="list-style-type: none"> • Weekly, or more frequent visits recommended for the first month 	

Patient Name: _____



APPROPRIATE USE CHECKLIST:
BUPRENORPHINE-CONTAINING TRANSMUCOSAL PRODUCTS FOR OPIOID DEPENDENCE

This checklist may be used for visits following the induction period and filed in patient's medical record to document safe use conditions.

MEASUREMENT TO ENSURE APPROPRIATE USE	NOTES
Date: Visit #	
MAINTENANCE	
<input type="checkbox"/> Assessed and encouraged patient to take medication as prescribed • Consider pill/film count/dose reconciliation	
<input type="checkbox"/> Assessed appropriateness of dosage • Buprenorphine combined with naloxone is recommended for maintenance: <ul style="list-style-type: none"> • Generic formulations of Suboxone®: doses ranging from 12 mg to 16 mg of buprenorphine are recommended for maintenance • Zubsolv®: a target dose of 11.4 mg buprenorphine is recommended for maintenance • Bunavail™: a target dose of 8.4 mg of buprenorphine is recommended for maintenance • Doses higher than this should be an exception • The need for higher dose should be carefully evaluated	
<input type="checkbox"/> Conduct urine drug screens as appropriate to assess use of illicit substances	
<input type="checkbox"/> Assessed participation in professional counseling and support services	
<input type="checkbox"/> Assessed whether benefits of treatment with buprenorphine-containing products outweigh risks associated with buprenorphine-containing products	
<input type="checkbox"/> Assessed whether patient is making adequate progress toward treatment goals • Considered results of urine drug screens as part of the evidence of the patient complying with the treatment program • Consider referral to more intensive forms of treatment for patients not making progress	
<input type="checkbox"/> Scheduled next visit at interval commensurate with patient stability • Weekly, or more frequent visits are recommended for the first month	



OFFICE-BASED BUPRENORPHINE THERAPY FOR OPIOID DEPENDENCE:

IMPORTANT INFORMATION FOR PRESCRIBERS

BUPRENORPHINE-CONTAINING TRANSMUCOSAL PRODUCTS

I. INTRODUCTION

The purpose of this brochure is to provide information about the Risk Evaluation and Mitigation Strategy (REMS) to prescribers of buprenorphine-containing oral transmucosal products who are certified to treat opioid dependence under the Drug Addiction Treatment Act of 2000 (DATA 2000). This REMS applies to buprenorphine-containing oral transmucosal products indicated for the treatment of opioid dependence and buprenorphine-containing products indicated for the treatment of opioid dependence with the same types of safety concerns as the oral transmucosal products (hereinafter, "buprenorphine-containing products"). This REMS does not apply to buprenorphine-containing products that are dispensed to patients admitted to an Opioid Treatment Program (OTP) under 42 CFR Part 8.

The products covered in this REMS¹ are:

- Generic equivalents of Subutex® (buprenorphine hydrochloride) sublingual tablet
- Generic equivalents of Suboxone® (buprenorphine hydrochloride/naloxone hydrochloride) sublingual tablet
- Zubsolv® (buprenorphine/naloxone) sublingual tablet
- Bunavail™ (buprenorphine hydrochloride/naloxone hydrochloride) buccal film

This brochure summarizes important safety issues and messages needed to manage and counsel patients about safe use of these products.

What are buprenorphine-containing products?

Buprenorphine-containing products are available both as products containing the single active ingredient, buprenorphine, and products that combine buprenorphine with naloxone.

Buprenorphine-containing products containing the single active ingredient buprenorphine are indicated for the treatment of opioid dependence and are preferred for induction.

Some buprenorphine-containing products include a second active ingredient, naloxone HCl, intended to deter individuals from abusing buprenorphine-containing products by the intravenous route.

Sublingual tablet formulations containing buprenorphine with naloxone are indicated for the maintenance treatment of opioid dependence. The Suboxone sublingual film formulation contains buprenorphine with naloxone and is indicated for the induction of patients physically dependent on heroin or other short-acting opioids (for long-acting opioids, see next section) and maintenance treatment of opioid dependence.

Buprenorphine-containing products are used as part of a complete treatment plan, including counseling and psychosocial support.

What are the primary differences among the buprenorphine products that contain naloxone?

The primary differences are the available dosage strengths, recommended doses, indications, and formulations. The available dosage strengths and recommended doses vary based on the bioavailability for each product (i.e., how much of the buprenorphine is absorbed after administration).

Available Dosage Strengths:

Table 1

Subutex (Buprenorphine sublingual tablets), including generic equivalents:	2 mg buprenorphine 8 mg buprenorphine
Suboxone (Buprenorphine and naloxone sublingual tablets), including generic equivalents:	2 mg buprenorphine / 0.5 mg naloxone 8 mg buprenorphine / 2 mg naloxone
Zubsolv (Buprenorphine and naloxone sublingual tablets):	1.4 mg buprenorphine / 0.36 mg naloxone 5.7 mg buprenorphine / 1.4 mg naloxone 8.6 mg buprenorphine / 2.1 mg naloxone 11.4 mg buprenorphine / 2.9 mg naloxone
Suboxone sublingual film (Buprenorphine and naloxone sublingual film):	2 mg buprenorphine / 0.5 mg naloxone 4 mg buprenorphine / 1 mg naloxone 8 mg buprenorphine / 2 mg naloxone 12 mg buprenorphine / 3 mg naloxone
Bunavail (Buprenorphine hydrochloride and naloxone hydrochloride buccal film):	2.1 mg buprenorphine / 0.3 mg naloxone 4.2 mg buprenorphine / 0.7 mg naloxone 6.3 mg buprenorphine / 1 mg naloxone

Indications:

Buprenorphine-only sublingual tablets (Subutex and generic equivalents) are indicated for the treatment of opioid dependence and are preferred for induction.

The Suboxone sublingual film formulation may be used for induction in patients physically dependent on heroin or other short-acting opioids as well as for maintenance. However, buprenorphine-only products are preferred for patients physically dependent on methadone or long-acting opioids taken as per approved labeling.

The following buprenorphine and naloxone combination products are indicated for the maintenance treatment of opioid dependence after initial induction:

- buprenorphine/naloxone sublingual tablets (generic equivalents of Suboxone)
- Zubsolv sublingual tablets
- Bunavail buccal film
- Suboxone sublingual film

Corresponding doses of buprenorphine products that contain naloxone:

Patients being switched between different formulations should be started on the corresponding dose (as shown in Table 2 below) compared to the previously administered product. Patients should be monitored for symptoms related to over-dosing or under-dosing and dosing adjustments should be made as clinically indicated².

¹ Buprenorphine hydrochloride sublingual tablets marketed under the trade name Subutex® and buprenorphine hydrochloride/naloxone hydrochloride sublingual tablets and sublingual film marketed under the trade name Suboxone® are covered under the Subutex and Suboxone REMS programs.

² Note that, although the nominal Suboxone sublingual film doses are the same as the Suboxone sublingual tablets and generic equivalent tablets, not all strengths and combinations of the films are bioequivalent to the generic equivalent or Zubsolv tablets. Therefore, systemic exposures of buprenorphine and naloxone may be different when patients are switched from tablets to films or vice-versa.

Table 2

Corresponding doses of buprenorphine products that contain naloxone			
Suboxone sublingual tablets, including generic equivalents	Suboxone sublingual films	Zubsolv sublingual tablets	Bunavail buccal films
2 mg buprenorphine/ 0.5 mg naloxone	2 mg buprenorphine/ 0.5 mg naloxone	1.4 mg buprenorphine/ 0.36 mg naloxone	
	4 mg buprenorphine/ 1 mg naloxone		2.1 mg buprenorphine/ 0.3 mg naloxone
8 mg buprenorphine/ 2 mg naloxone	8 mg buprenorphine/ 2 mg naloxone	5.7 mg buprenorphine/ 1.4 mg naloxone	4.2 mg buprenorphine/ 0.7 mg naloxone
	12 mg buprenorphine/ 3 mg naloxone	8.6 mg buprenorphine/ 2.1 mg naloxone	6.3 mg buprenorphine/ 1 mg naloxone
		11.4 mg buprenorphine/ 2.9 mg naloxone	

II. REMS – RISK EVALUATION AND MITIGATION STRATEGY

What is a Risk Evaluation and Mitigation Strategy (REMS)?

A REMS is a strategy to manage a known or potential risk associated with a drug. A REMS can include, among other strategies, a Medication Guide, a communication plan, and elements to assure safe use.

Is there a REMS for buprenorphine-containing products?

Yes, a REMS has been implemented as part of the FDA requirements to ensure that the benefits of treatment with buprenorphine-containing products outweigh the potential risks.

The following products are covered under the Buprenorphine-containing Transmucosal products for Opioid Dependence (BTOD) REMS Program:

- Generic equivalents of Subutex® (buprenorphine hydrochloride) sublingual tablet
- Generic equivalents of Suboxone® (buprenorphine hydrochloride/naloxone hydrochloride) sublingual tablet
- Zubsolv® (buprenorphine/naloxone) sublingual tablet
- Bunavail™ (buprenorphine hydrochloride/naloxone hydrochloride) buccal film

The goals of the BTOD REMS are to:

- Mitigate the risks of accidental overdose, misuse, and abuse
- Inform prescribers, pharmacists, and patients of the serious risks associated with the use of buprenorphine-containing products

What is my role with regard to the BTOD REMS?

To meet the requirements of the REMS and to ensure the benefits of prescribing buprenorphine-containing products outweigh the risks of accidental overdose, misuse, and abuse. Prescribers should take the following measures and document actions taken with each patient to ensure safe use conditions:

- Verify the patient meets diagnostic criteria for opioid dependence
- Discuss the risks associated with buprenorphine-containing products, including those described in the Medication Guide
- Provide induction doses under appropriate supervision
- Prescribe a limited amount of medication to the patient that will last until the next visit
- Explain how to safely store the medication out of reach of children
- Schedule patient appointments commensurate with patient stability (weekly or more frequent visits recommended for the first month)
- Consider “pill/film count”/dose reconciliation
- Assess whether patient is receiving counseling/psychosocial support considered necessary for treatment
- Assess whether patient is making progress toward treatment goals (including, as appropriate, urine toxicology testing)
- Continually assess appropriateness of maintenance dose
- Continually assess whether or not benefits of treatment outweigh the risks

As part of the BTOD REMS, prescribers of buprenorphine-containing products should document safe use conditions and that each patient has received the required clinical monitoring using the [Appropriate Use Checklist](#), or by using another method/system (e.g. electronic health record) specific to the prescriber's office practice. This can be retained in the records of each patient. Additional copies of the [Appropriate Use Checklist](#) can be obtained online at www.btodrems.com or by calling 1-855-223-3922.

III. HIGHLIGHTED IMPORTANT SAFETY INFORMATION FOR BUPRENORPHINE-CONTAINING PRODUCTS

This section of the brochure highlights important safety information to consider when prescribing buprenorphine-containing products **Refer to the Full Prescribing Information (FPI) for detailed safety-related information for buprenorphine-containing products.**

Abuse Potential for Buprenorphine-Containing Products

Are buprenorphine-containing products abusable?

Yes, buprenorphine, like morphine and other opioids, has the potential for being abused and is subject to criminal diversion. This should be considered when prescribing or dispensing buprenorphine in situations when the clinician is concerned about an increased risk of misuse, abuse, or diversion. Healthcare professionals should contact their state professional licensing board or state controlled substances authority for information on how to prevent and detect abuse, misuse, or diversion of this product.

Abuse of buprenorphine poses a risk of overdose and death. This risk is increased with the concomitant use of buprenorphine and alcohol and other substances, especially benzodiazepines.

The prescriber may be able to more easily detect misuse or diversion by maintaining records of medication prescribed including date, dose, quantity, frequency of refills, and renewal request of medication prescribed.

Proper assessment of the patient, proper prescribing practices, periodic re-evaluation of therapy, and proper handling and storage of the medication by the prescriber and patient are appropriate measures that help to limit abuse of opioid drugs.

Due to the partial agonist properties of buprenorphine, buprenorphine-containing products may precipitate opioid withdrawal signs and symptoms in persons dependent on full opioid agonists if administered before the agonist effects of the opioid have subsided. However, buprenorphine products that contain naloxone are highly likely to produce marked and intense withdrawal signs and symptoms if misused parenterally by individuals dependent on full opioid agonists such as heroin, morphine, or methadone. Therefore, to discourage misuse or abuse, it is highly recommended that, after induction, for unsupervised administration, buprenorphine with naloxone rather than buprenorphine alone is prescribed whenever feasible.

However, clinicians should also be aware that some opioid-dependent persons can and do abuse buprenorphine/naloxone combinations by the intravenous or intranasal routes. This is especially true for opioid-dependent persons with a low level of full mu-opioid physical dependence or those whose opioid physical dependence is predominantly to buprenorphine. Patients who continue to misuse, abuse, or divert buprenorphine products or other opioids should be provided with, or referred to, more intensive and structured treatment.

Can buprenorphine-containing products cause dependence?

Yes, buprenorphine is a partial agonist at the mu-opioid receptor. Chronic administration produces dependence of the opioid type, characterized by withdrawal upon abrupt discontinuation or rapid taper. The withdrawal syndrome is milder than seen with full agonists, and may be delayed in onset. If cessation of therapy is indicated, it is appropriate to taper the buprenorphine dose, rather than abruptly discontinue the medication. Buprenorphine can be abused in a manner similar to other opioids, legal or illicit. This should be considered when prescribing or dispensing buprenorphine in situations where there is an increased concern about the possibility of misuse, diversion, or abuse.

What precautions should I take in my practice to prevent diversion and abuse?

You should consider the following suggestions:

- Initiate treatment with supervised administration, progressing to unsupervised administration as your patient's clinical stability permits
- Limit the use of buprenorphine-only products, such as buprenorphine sublingual tablets, to supervised use, wherever possible. Point out to the patient that some buprenorphine-containing products also contain naloxone. The naloxone is likely to precipitate withdrawal signs and symptoms when injected by individuals dependent on heroin, morphine, or other full opiate agonists. It is strongly recommended that buprenorphine/naloxone products be used whenever unsupervised administration is planned
- As your patients progress beyond induction to a stabilized dose, consider a longer-term prescription of buprenorphine-containing product to be taken at home. When determining the quantity of buprenorphine-containing product to be prescribed, you should consider your patient's level of stability, the security of his or her

home situation, and other factors likely to affect the ability to manage supplies of medication in an unsupervised environment

- Check the applicable state Prescription Drug Monitoring Programs, where practical, to identify behaviors that may represent abuse.
- Have plans in place to deal with patient requests for replacement of prescriptions or supplies of medication that are described as lost or stolen
- Keep tight control of your prescription pads. Never leave them in the examination room, even inside a desk drawer. Never sign an incomplete prescription blank
- Write all numbers (quantity and strength) in both numbers and letters - like you would write a personal check
- Establish a relationship with the pharmacies you expect to be filling your prescriptions. Discuss potential diversion problems and controls with them
- Maintain copies of photo (or other) I.D. and Social Security numbers in patients' records
- If you suspect an attempt to divert prescription medications, unsupervised administration privileges should be reevaluated. Carefully consider options such as random drug testing or a callback to verify adherence to program rules. In a callback, the patient receives an unannounced phone call and must show up at the prescriber's office within a reasonable period (e.g., 24 to 36 hours) with all prescribed medications. In this case, the amount of medication remaining must correspond to the amount expected based on prescribed dosing. If this program is implemented, prescribers should clearly state their policy to patients in advance.

Buprenorphine, like morphine and other opioids, has the potential for being abused and is subject to criminal diversion. Patients who continue to misuse, abuse, or divert buprenorphine products or other opioids, despite implementation of the above precautions, should be provided or referred for more intensive and structured treatment.

How can patients prevent accidental exposure to buprenorphine-containing products in children?

Patients should be instructed to keep buprenorphine-containing products in a secure place, out of the sight and reach of children and other household members. Accidental or deliberate ingestion by a child may cause respiratory depression that can result in death. If a child is exposed accidentally to a buprenorphine-containing product, seek immediate urgent medical attention.

What is an appropriate medical response to overdose on buprenorphine-containing product?

In the case of overdose, the primary management should be the re-establishment of adequate ventilation with mechanical assistance of respiration, if required. Naloxone hydrochloride may be of value for the management of buprenorphine overdose. Higher than normal doses and repeated administration may be necessary.

Contraindications

- Hypersensitivity to buprenorphine and, in the case of combination products, naloxone

Warnings and Precautions

- Buprenorphine can be abused in a similar manner to other opioids. Clinical monitoring appropriate to the patient's level of stability is essential. Multiple refills should not be prescribed early in treatment or without appropriate patient follow-up visits
- Significant respiratory depression and death have occurred in association with buprenorphine, particularly when taken by the intravenous (IV) route in combination with benzodiazepines or other CNS depressants (including alcohol)
- Consider dose reduction of CNS depressants, buprenorphine-containing products, or both in situations of concomitant prescription
- Store buprenorphine-containing products safely out of the sight and reach of children. Buprenorphine can cause severe, possibly fatal, respiratory depression in children
- Chronic administration produces opioid-type physical dependence. Abrupt discontinuation or rapid dose taper may result in opioid withdrawal syndrome
- Monitor liver function tests prior to initiation and during treatment and evaluate suspected hepatic events
- Do not administer buprenorphine-containing products to patients with known hypersensitivity to buprenorphine or, in the case of combination products, naloxone
- An opioid withdrawal syndrome is likely to occur with parenteral misuse of buprenorphine-containing products by individuals physically dependent on full opioid agonists before the agonist effects of other opioids have subsided, particularly buprenorphine-containing products that also contain naloxone.
- Neonatal withdrawal has been reported following use of buprenorphine by the mother during pregnancy
- Buprenorphine-containing products covered under the BTOD REMS are not appropriate as an analgesic. There have been reported deaths of opioid naive individuals who received a 2 mg sublingual dose
- Caution patients about the risk of driving or operating hazardous machinery
- For buprenorphine/naloxone combination products:
 - Not recommended in patients with **severe** hepatic impairment
 - Not recommended for initiation of treatment (induction) in patients with **moderate** hepatic impairment due to the increased risk of precipitated withdrawal. However, buprenorphine/naloxone products may be used with caution for maintenance treatment in patients with **moderate** hepatic impairment who have initiated treatment on a buprenorphine product without naloxone. However, patients should be carefully monitored and consideration given to the possibility of naloxone interfering with buprenorphine's efficacy.
- For buprenorphine sublingual tablets:
 - **Severe** hepatic impairment: Consider reducing the starting and titration incremental dose by half compared to patients with normal liver function, and monitor for

signs and symptoms of toxicity or overdose caused by increased levels of buprenorphine.

- **Moderate** hepatic impairment: Although no dose adjustment is necessary for patients with moderate hepatic impairment, buprenorphine sublingual tablets should be used with caution in these patients and prescribers should monitor patients for signs and symptoms of toxicity or overdose caused by increased levels of buprenorphine.

Adverse Reactions

- Adverse events most commonly observed with buprenorphine-containing products are headache, nausea, vomiting, hyperhidrosis, constipation, signs and symptoms of withdrawal, insomnia, and pain. For a complete list of potential adverse events associated with buprenorphine-containing products, please see the Full Prescribing Information.
- To report SUSPECTED ADVERSE REACTIONS, contact
 - The manufacturer of the product taken or
 - FDA MedWatch program by phone at 1-800-FDA-1088 or online at www.fda.gov/medwatch/report.htm

Drug Interactions

- Monitor patients starting or ending CYP3A4 inhibitors or inducers for potential over or under dosing
- Use caution in prescribing buprenorphine-containing products for patients receiving benzodiazepines or other CNS depressants and warn patients against concomitant self-administration/misuse

Use in Specific Populations

- **Pregnancy:** Based on animal data, buprenorphine may cause fetal harm. Buprenorphine-containing products are not indicated for use during pregnancy unless potential benefit justifies potential risk
- **Nursing mothers:** Caution should be exercised when buprenorphine-containing products are administered to a nursing woman.
- Safety and effectiveness of buprenorphine-containing products in patients below the age of 16 have not been established
- Administer these products with caution to elderly or debilitated patients
- Buprenorphine/naloxone products are not recommended for use in patients with severe hepatic impairment and may not be appropriate for patients with moderate hepatic impairment.
- Buprenorphine-only sublingual tablets should be used with caution in patients with moderate to severe hepatic impairment and a dose adjustment is recommended for patients with severe hepatic impairment.

IV. PRESCRIBING BUPRENORPHINE-CONTAINING PRODUCTS

When should products containing buprenorphine with naloxone be prescribed?

Buprenorphine products that include naloxone are indicated for maintenance treatment of opioid dependence and are preferred over buprenorphine-only products for unsupervised administration. Suboxone sublingual film, which includes naloxone, is indicated for the induction of patients physically dependent on heroin or other short-acting opioids (for long-acting opioids, see discussion below and in Introduction Section) and maintenance treatment of opioid dependence.

What is the proper protocol for induction?

Prior to induction, consideration should be given to the type of opioid dependence (i.e. long- or short-acting opioid), the time since last opioid use, and the degree or level of opioid dependence.

In some studies, gradual induction over several days led to a high rate of drop-out of buprenorphine patients during the induction period. Therefore, it is recommended that an adequate maintenance dose, titrated to clinical effectiveness, should be achieved as rapidly as possible to prevent undue opioid withdrawal signs and symptoms.

Patients taking methadone or long-acting opioids:

Buprenorphine monotherapy is preferred for induction in patients physically dependent on methadone or long-acting opioids, if taken per approved labeling. Buprenorphine and naloxone combination products have not been evaluated in adequate and well-controlled studies for induction in patients on long-acting opioids, who appear to be more likely to experience precipitated and prolonged withdrawal than those on short-acting opioids.

To avoid inadvertently precipitating opioid withdrawal, induction should be undertaken when clear and obvious signs of withdrawal are evident. A clinical tool to assess withdrawal should be used. For example, the Clinical Opioid Withdrawal Scale (COWS) can be used and a score of ≥ 12 should be recorded on the COWS before the first dose is administered.

Patients taking heroin or other short-acting opioids:

Patients physically dependent on heroin or other short-acting opioids may initiate treatment with either a buprenorphine-only sublingual product or with Suboxone sublingual film. At treatment initiation, the dose of buprenorphine-only sublingual product or Suboxone sublingual film should be administered when moderate signs of opioid withdrawal are evident and at least 6 hours after the patient last used short-acting opioids.

How should I schedule office visits: how much involvement should I have?

During the induction period, it is recommended that the initial dose(s) be provided under supervision and that no more than 1 to 2 days of products containing buprenorphine alone for take-home use be provided on each of the 2 to 3 visits during the first week of treatment.

Patients should be seen at reasonable intervals (e.g., at least weekly during the first month of treatment) based upon the individual

circumstances of the patient. Products containing buprenorphine with naloxone should be prescribed in consideration of the frequency of visits. Provision of multiple refills is not advised early in treatment or without appropriate patient follow-up visits. Periodic assessment is necessary to determine compliance with the dosing regimen, effectiveness of the treatment plan, and overall patient assessment.

Once a stable dosage has been achieved and toxicological tests do not indicate illicit drug use, less frequent follow-up visits may be appropriate. A once-monthly visit schedule may be reasonable for patients on a stable dosage of products containing buprenorphine with naloxone who are making progress toward the treatment objectives. Continuation or modification of pharmacotherapy should be based on the prescriber's evaluation of treatment outcomes and objectives such as:

1. Absence of buprenorphine toxicity
2. Absence of medical or behavioral adverse effects
3. Responsible handling of buprenorphine-containing product by the patient
4. Patient's compliance with all elements of the treatment plan (including recovery-oriented activities, psychotherapy, and/or other psychosocial modalities)
5. Abstinence from illicit drug use (including problematic alcohol and/or benzodiazepine use)

If treatment goals are not being achieved, the prescriber should reevaluate the appropriateness of continued treatment. Patients who continue to misuse, abuse or divert buprenorphine products or other opioids should be provided with, or referred to, more intensive and structured treatment.

How do I manage in-office induction doses without maintaining a supply in my office?

For those prescribers who do not wish to maintain a supply of buprenorphine-containing products in their offices, it is important to develop a good working relationship with your local pharmacies. To ensure that you will be able to exchange information with the pharmacist, such as confirming the validity of your induction prescriptions, it is recommended that you have the patient sign a release of information at the time of the initial office visit. A sample consent form with all the elements required under 42 CFR Part 2.31 is included in [Appendix A](#) of this brochure.

On the day of induction, write a prescription **only** for the induction day's dosage. Instruct your patient (or, if available, a trustworthy family member accompanying the patient) to take the prescription to the pharmacy, have it filled and bring it back to your office for dosing.

It is recommended that you call or fax ahead to the pharmacy to ensure availability of the medication and to reduce patient waiting time. You should instruct the patient not to take the dose until he or she returns to the office. The induction dose will be administered, and he or she will be monitored, in your office. The pharmacist should reiterate this instruction upon filling the prescription.

Note that it is illegal for prescribers to hold medication in the office that is prescribed for a specific patient. Therefore, you should limit the prescription to one day's dose, and repeat this method for the

first several days of treatment before providing a prescription for several days' supply at one time.

Will prescriptions be valid at any pharmacy, or will I need to refer patients to a specific location?

Prescriptions specifying a buprenorphine-containing product will be valid at any pharmacy authorized by DEA to handle schedule III controlled substances. However, prior to prescribing buprenorphine-containing products it is essential that you establish a relationship with one or more specific pharmacies in your area that will be in a position to provide your patients with initial doses, as well as instructions for returning to your office for induction and the follow-up prescription.

Generally, a pharmacy near your office is recommended for patient convenience.

What storage and record-keeping requirements are associated with treating patients for opioid dependence with buprenorphine-containing products?

If you wish to maintain a supply of buprenorphine-containing products in your office for the purpose of dispensing to patients during induction, you will be required to keep the medications in a secure environment. According to federal requirement, they must be kept in a securely locked, substantially constructed cabinet. You will also be required to maintain a written record of the disposition of all doses. Usually this can be done with the maintenance of a logbook in which you record all incoming doses and account for each dispensed dose as it is used. This record must be kept current at all times. Additional requirements may be in place in your state. You are also required to take an inventory every 2 years, and to keep records of all receipts.

In addition, prescribers of buprenorphine-containing products should keep accurate and complete records for each patient that include:

1. The medical history and physical examination
2. Diagnostic, therapeutic, and laboratory results
3. Evaluations and consultations
4. Treatment objectives
5. Discussion of risks and benefits
6. All treatments that the patient is receiving
7. Medications (including date, type, dosage, and quantity prescribed and/or dispensed to each patient)
8. A physical inventory of all Schedule III, IV, and V controlled substances on hand that are dispensed by the prescriber in the course of maintenance or detoxification treatment of an individual
9. Instructions and agreements
10. Periodic reviews

Records should remain current and be maintained in an accessible manner and readily available for review. Prescribers must adhere to the special confidentiality requirements of 42 CFR Part 2.

Are there special confidentiality issues I should consider?

Remember that you may be communicating with the pharmacist to verify prescriptions for a particular patient. There are special federal regulations concerning the confidentiality of substance abuse

treatment records (42 CFR Part 2), and the privacy of health records (Health Insurance Portability and Accountability Act [HIPAA]). To ensure that you will be able to exchange information with the pharmacist, such as confirming the validity of a prescription for a buprenorphine-containing product, it is recommended that you have the patient sign a release of information at the time of the initial office visit.

A sample consent form with all the elements required under 42 CFR Part 2.31 is included in [Appendix A](#) of this brochure. It is particularly important to obtain the patient's consent if you elect to phone or fax in prescriptions, as this constitutes disclosure of the patient's treatment. When the prescription is directly transmitted by the prescriber, there are also prohibitions on the further redisclosure of patient identifying information by the pharmacist. 42 CFR Part 2.31 does not apply when it is the patient who delivers the prescription to the pharmacist, without direct communication from the prescriber to the pharmacist.

To learn more about these regulations, visit the SAMHSA website, <http://buprenorphine.samhsa.gov>, or call 1-866-BUP-CSAT (1-866-287-2728).

Dosing and Administration of Buprenorphine-containing Products**How do I maintain clinically effective dosing for stabilized patients?**

The recommended target dose is 16 mg buprenorphine/4 mg naloxone per day for Suboxone sublingual tablets and sublingual film, including generic equivalents, and is 11.4 mg buprenorphine/2.8 mg naloxone per day for Zubsolv sublingual tablet, and 8.4 mg buprenorphine/1.4 mg naloxone per day for Bunavail buccal film. Clinical studies have shown that these are clinically effective doses. Although lower doses may be effective in some patients, for most patients, this dose should alleviate withdrawal symptoms and block or attenuate the effects of other opioid agonists for at least 24 hours.

The upper limit of the recommended dose is 24 mg per day for Suboxone sublingual tablets and sublingual film, including generic equivalents, 17.1 mg per day for Zubsolv, and 12.6 mg per day for Bunavail. The reported lack of significant increase in brain mu-receptor occupancy between the target dose and twice the target dose implies that there should be little difference in clinical effectiveness at doses between the target dose and the recommended upper limit daily dose. When a patient expresses a need for a higher dose, consider the possible causes (e.g., environmental stressors or psychosocial issues that increase cravings or possible drug interactions). Before increasing the patient's dose, explore other alternatives. Also consider the possibility that the patient may be exaggerating symptoms to obtain additional medication for diversion.

How are buprenorphine-containing products supplied?

Subutex (Buprenorphine sublingual tablets), including generic equivalents:	2 mg buprenorphine 8 mg buprenorphine
Suboxone (Buprenorphine and naloxone sublingual tablets), including generic equivalents:	2 mg buprenorphine / 0.5 mg naloxone 8 mg buprenorphine / 2 mg naloxone
Zubsolv (Buprenorphine and naloxone sublingual tablets):	1.4 mg buprenorphine / 0.36 mg naloxone 5.7 mg buprenorphine / 1.4 mg naloxone 8.6 mg buprenorphine / 2.1 mg naloxone 11.4 mg buprenorphine / 2.9 mg naloxone
Suboxone sublingual film (Buprenorphine and naloxone sublingual film):	2 mg buprenorphine / 0.5 mg naloxone 4 mg buprenorphine / 1 mg naloxone 8 mg buprenorphine / 2 mg naloxone 12 mg buprenorphine / 3 mg naloxone
Bunavail (Buprenorphine hydrochloride and naloxone hydrochloride buccal film):	2.1 mg buprenorphine / 0.3 mg naloxone 4.2 mg buprenorphine / 0.7 mg naloxone 6.3 mg buprenorphine / 1 mg naloxone

How should buprenorphine with or without naloxone be administered?

For buprenorphine-containing tablets, the patient should place tablets under the tongue until they are dissolved. For doses requiring the use of more than 2 tablets, patients are advised to either place all the tablets at once or alternatively (if they cannot fit in more than 2 tablets comfortably), place 2 tablets at a time under the tongue. Either way, the patients should continue to hold the tablets under the tongue until they dissolve; swallowing the tablets reduces the bioavailability of the drug. To ensure consistency in bioavailability, patients should follow the same manner of dosing with continued use of the product.

For Bunavail buccal film administration, the patient should use the tongue to wet the inside of the cheek or rinse the mouth with water to moisten the area immediately before placement of Bunavail; open the Bunavail package immediately prior to use as indicated by the instructions; place the Bunavail film near the tip of a dry finger with the text facing up; place the side of the Bunavail film with the text against the inside of the cheek; press and hold the film in place for 5 seconds. Bunavail film(s) adhere to the moist buccal mucosa and should stay in place after this period.

If multiple films need to be administered, the patient should immediately apply the next film. Note that when two films are required for one dose, the patient should place one film on the inside of each cheek. For doses requiring multiple films, no more than two films should be applied to the inside of one cheek at a time. The patient should be instructed to avoid manipulating the film(s) with their tongue or finger(s) and avoid drinking or eating food until the film(s) dissolve.

For Suboxone sublingual film, the patient should place the Suboxone film under the tongue. If an additional film is necessary to achieve the prescribed dose, the additional film should be placed sublingually on the opposite side from the first film. If an additional third film is needed, place it sublingually after the first 2 Suboxone sublingual films have dissolved. Place Suboxone sublingual films in a manner to minimize overlapping as much as possible. Keep the films under the tongue, close to the base on the left or right side, until they are completely dissolved. Suboxone sublingual film should NOT be chewed, swallowed, or moved after placement.

How should I manage patients who are not compliant with therapy?

Prescribers will need to decide when they cannot appropriately provide further management for particular patients. For example, some patients may be abusing or dependent on various drugs, or unresponsive to psychosocial intervention, such that the prescriber does not feel that he or she has the expertise to manage the patient. In such cases, the prescriber may want to assess whether to refer the patient to a specialist and/or more intensive behavioral treatment environment. Decisions should be based on a treatment plan established and agreed upon with the patient at the beginning of treatment.

Discontinuing Therapy with Buprenorphine-Containing Products

What can I tell patients who wish to discontinue treatment?

Patients should be advised not to change the dose of buprenorphine-containing products without consulting their prescriber. Patients seeking to discontinue treatment with buprenorphine-containing products for opioid dependence should be apprised of the potential to relapse to illicit drug use associated with discontinuation of opioid agonist medication-assisted treatment.

If a dependent patient abruptly discontinues use of these products, an opioid abstinence or withdrawal syndrome may develop. If cessation of therapy is indicated, it may be appropriate to taper the dose of these products, rather than abruptly discontinue it. The prescriber can provide a dose schedule to accomplish a gradual discontinuation of the medication.

V. PSYCHOSOCIAL SUPPORT AND OTHER PATIENT COUNSELING

How important is counseling for my patients and my practice?

Pharmacotherapy is only one aspect of treatment. Psychosocial counseling is an essential component of treatment for opioid dependence. Because it is such a crucial element, DATA 2000 requires that prescribers seeking to obtain the certification to prescribe buprenorphine-containing products must be able to provide or refer patients for counseling.

In addition to services typically provided by prescribers, counseling may incorporate such elements as motivational enhancement therapy, cognitive behavioral therapy, prevention education, and intervention in case of relapse.

If counseling is provided by an individual other than the prescriber, it is essential that the counselor partner with the prescriber in providing care. The counselor can provide an additional measure of monitoring for adherence and treatment response.

What information about the safe use of buprenorphine-containing products needs to be communicated to patients?

Review the contents of the Medication Guide, in its entirety, with each patient, including the following:

- Warn patients that it is extremely dangerous to self-administer non-prescribed benzodiazepines or other CNS depressants

(including alcohol) while taking any buprenorphine-containing product. Patients prescribed benzodiazepines or other CNS depressants should be cautioned to use them only as directed by their prescriber.

- Instruct patients to keep buprenorphine-containing products in a secure place, out of the sight and reach of children. Accidental or deliberate ingestion by a child may cause respiratory depression that can result in death. If a child is exposed to one of these products, medical attention should be sought immediately.
- Advise patients that buprenorphine-containing products contain an opioid that can be a target for people who abuse prescription medications or street drugs. Patients should be cautioned to keep their products in a safe place, and to protect them from theft.
- Instruct patients never to give buprenorphine-containing products to anyone else, even if he or she has the same signs and symptoms. It may cause harm or death.
- Advise patients that selling or giving away buprenorphine-containing products is against the law.
- Caution patients that buprenorphine-containing products may impair the mental or physical abilities required for the performance of potentially dangerous tasks, such as driving or operating machinery. Caution should be taken especially during induction and dose adjustments and until patients are reasonably certain that therapy with a buprenorphine-containing product does not adversely affect their ability to engage in such activities.
- Advise patients not to change the dose of the buprenorphine-containing product without consulting their prescriber.
- Advise patients to take the buprenorphine-containing product once a day as directed.
- Inform patients that the buprenorphine-containing products can cause drug dependence of the opioid type. Withdrawal signs and symptoms may occur when the medication is discontinued.
- Advise patients seeking to discontinue treatment with the buprenorphine-containing product for opioid dependence to work closely with their prescriber on a tapering schedule and apprise them of the potential to relapse to illicit drug use associated with discontinuation of opioid agonist/partial agonist medication-assisted treatment.
- Caution patients that, like other opioids, buprenorphine-containing products may produce orthostatic hypotension in ambulatory individuals.
- Ask patients if other prescription medications, over-the-counter medications, or herbal preparations are prescribed or currently being used.
- Advise patients who become pregnant, or are planning to become pregnant, to consult their prescriber regarding the possible effects of using buprenorphine-containing products during pregnancy.
- Buprenorphine-containing products should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

- Based on two studies in 13 lactating women, buprenorphine and its metabolite norbuprenorphine are present in low levels in human milk and infant urine, and available data have not shown adverse reactions in breastfed infants. There are no data on the combination product buprenorphine/naloxone in breastfeeding; however oral absorption of naloxone is minimal. Caution should be exercised when buprenorphine-containing products are administered to a nursing woman. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for buprenorphine-containing products and any potential adverse effects on the breastfed child from the drug or from the underlying maternal condition.
- Advise the nursing mother taking buprenorphine-containing products to monitor the infant for increased drowsiness and breathing difficulties.
- Ask patients to inform their family members or other appropriate individuals that, in the event of emergency, the treating prescriber or emergency department staff should be informed that the patient is physically dependent on an opioid and that the patient is being treated with a buprenorphine-containing product
- Instruct patients to dispose of unused buprenorphine-containing product as soon as it is no longer needed. Unused tablets and films (after they have been removed from the foil package) should be flushed down the toilet.

VI. WHERE CAN I GET MORE INFORMATION ON TREATING PATIENTS WITH BUPRENORPHINE-CONTAINING PRODUCTS?

Refer to the package insert for Full Prescribing Information, which can be found at www.btodrems.com.

Additional recommendations may be found in treatment guidelines available free from the Center for Substance Abuse Treatment (CSAT) at the Substance Abuse and Mental Health Services Administration. Additional information is also available on the CSAT Buprenorphine Information Center website at <http://buprenorphine.samhsa.gov>.

General information about buprenorphine treatment and treatment of addiction are available through numerous sources including, but not limited to:

- American Society of Addiction Medicine website (www.asam.org)
- American Academy of Addiction Psychiatry website (www.aaap.org)
- Physician Clinical Support System - Buprenorphine (<http://pcssb.org>)

APPENDIX A

Sample 42 CFR Part 2.31 Consent Form

1. I (name of patient) _____
2. Authorize Dr. _____
3. To disclose any information needed to confirm the validity of my prescription and for submission for payment for the prescription.
4. To the dispensing pharmacy to whom I present my prescription or to whom my prescription is called/sent/faxed, as well as to third party payors.
5. For the purpose of assuring the pharmacy of the validity of the prescription, so it can be legally dispensed, and for payment purposes.
6. Date (on which this consent is signed)

7. Signature of patient

8. Signature of parent or guardian (where required)

9. Signature of person authorized to sign in lieu of the patient (where required)

10. This consent is subject to revocation at any time except to the extent that the program which is to make the disclosure has already taken action in reliance on it. If not previously revoked, this consent will terminate upon: (specify date, event, or condition, i.e. termination of treatment)

Notice to accompany disclosure:

Each disclosure made with the patient's written consent must be accompanied by the following written statement:

This information has been disclosed to you from records protected by Federal confidentiality rules (42 CFR Part 2). The Federal rules prohibit you from making any further disclosure of this information unless further disclosure is expressly permitted by the written consent of the person to whom it pertains or as otherwise permitted by 42 CFR Part 2. A general authorization for the release of medical or other information is NOT sufficient for this purpose. The Federal rules restrict any use of the information to criminally investigate or prosecute any alcohol or drug abuse patient.

For more information:

www.btodrems.com

BTOD REMS call center
(toll-free) 1-855-223-3922



OFFICE-BASED BUPRENORPHINE THERAPY FOR OPIOID DEPENDENCE: IMPORTANT INFORMATION FOR PHARMACISTS

BUPRENORPHINE-CONTAINING TRANSMUCOSAL PRODUCTS

I. INTRODUCTION

The purpose of this brochure is to provide pharmacists with information about the Risk Evaluation and Mitigation Strategy (REMS) for buprenorphine-containing products and the important safety issues and messages needed to counsel patients about its safe use. This REMS applies to buprenorphine-containing oral transmucosal products indicated for the treatment of opioid dependence and buprenorphine-containing products indicated for the treatment of opioid dependence with the same types of safety concerns as the oral transmucosal products (hereinafter, “buprenorphine-containing products”). This REMS does not apply to buprenorphine-containing products that are dispensed to patients admitted to an Opioid Treatment Program under 42 CFR Part 8.

The products covered in this REMS¹ are:

- Generic equivalents of Subutex® (buprenorphine hydrochloride) sublingual tablet
- Generic equivalents of Suboxone® (buprenorphine hydrochloride/naloxone hydrochloride) sublingual tablet
- Zubsolv® (buprenorphine/naloxone) sublingual tablet
- Bunavail™ (buprenorphine hydrochloride/naloxone hydrochloride) buccal film

What are buprenorphine-containing products?

Buprenorphine-containing products are available both as products containing the single active ingredient, buprenorphine, and products that combine buprenorphine with a second ingredient, naloxone.

Buprenorphine-containing products containing the single active ingredient buprenorphine are indicated for the treatment of opioid dependence and are preferred for induction.

Some buprenorphine products include a second active ingredient, naloxone HCl, intended to deter individuals from abusing buprenorphine-containing products by the intravenous route.

Sublingual tablet formulations containing buprenorphine with naloxone are indicated for the maintenance treatment of opioid dependence. The Suboxone sublingual film formulation contains buprenorphine with naloxone and is indicated for the induction of patients physically dependent on heroin or other short-acting opioids (for long-acting opioids, see next section) and maintenance treatment of opioid dependence.

Buprenorphine-containing products are used as part of a complete treatment plan, including counseling and psychosocial support.

What are the primary differences among the buprenorphine products that contain naloxone?

The primary differences are the available dosage strengths, recommended doses, indications, and formulations. The available dosage strengths and recommended doses vary based on the bioavailability for each product (i.e., how much of the buprenorphine is absorbed after administration).

Available Dosage Strengths:

Table 1

Subutex (Buprenorphine sublingual tablets), including generic equivalents:	2 mg buprenorphine 8 mg buprenorphine
Suboxone (Buprenorphine and naloxone sublingual tablets), including generic equivalents:	2 mg buprenorphine / 0.5 mg naloxone 8 mg buprenorphine / 2 mg naloxone
Zubsolv (Buprenorphine and naloxone sublingual tablets):	1.4 mg buprenorphine / 0.36 mg naloxone 5.7 mg buprenorphine / 1.4 mg naloxone 8.6 mg buprenorphine / 2.1 mg naloxone 11.4 mg buprenorphine / 2.9 mg naloxone
Suboxone sublingual film (Buprenorphine and naloxone sublingual film):	2 mg buprenorphine / 0.5 mg naloxone 4 mg buprenorphine / 1 mg naloxone 8 mg buprenorphine / 2 mg naloxone 12 mg buprenorphine / 3 mg naloxone
Bunavail (Buprenorphine hydrochloride and naloxone hydrochloride buccal film):	2.1 mg buprenorphine / 0.3 mg naloxone 4.2 mg buprenorphine / 0.7 mg naloxone 6.3 mg buprenorphine / 1 mg naloxone

When are buprenorphine-containing products prescribed?

Buprenorphine-only sublingual tablets (Subutex and generic equivalents) are indicated for the treatment of opioid dependence and are preferred for induction.

The Suboxone sublingual film formulation may be used for induction in patients physically dependent on heroin or other short-acting opioids as well as for maintenance. However, buprenorphine-only products are preferred for patients physically dependent on methadone or long-acting opioids taken as per approved labeling.

The following buprenorphine and naloxone combination products are indicated for the maintenance treatment of opioid dependence after initial induction:

- buprenorphine/naloxone sublingual tablets (generic equivalents of Suboxone)
- Zubsolv sublingual tablets
- Bunavail buccal film
- Suboxone sublingual film

Therefore, while you may see prescriptions for small amounts of buprenorphine alone presented for induction doses, you should expect the majority of prescriptions to be for buprenorphine with naloxone.

Buprenorphine-containing products are controlled as Schedule III narcotics under the Controlled Substances Act.

Patients being switched between different formulations should be started on the corresponding dose (as shown in Table 2 below) compared to the previously administered product. Patients should be monitored for symptoms related to over-dosing or under-dosing and dosing adjustments should be made as clinically indicated².

¹ Buprenorphine hydrochloride sublingual tablets marketed under the trade name Subutex® and buprenorphine hydrochloride/naloxone hydrochloride sublingual tablets and sublingual film marketed under the trade name Suboxone® are covered under the Subutex and Suboxone REMS programs.

² Note that, although the nominal Suboxone sublingual film doses are the same as the Suboxone sublingual tablets and generic equivalent tablets, not all strengths and combinations of the films are bioequivalent to the generic equivalent or Zubsolv tablets. Therefore, systemic exposures of buprenorphine and naloxone may be different when patients are switched from tablets to films or vice-versa.

Table 2

Corresponding doses of buprenorphine products that contain naloxone			
Suboxone sublingual tablets, including generic equivalents	Suboxone sublingual films	Zubsolv sublingual tablets	Bunavail buccal films
2 mg buprenorphine/ 0.5 mg naloxone	2 mg buprenorphine/ 0.5 mg naloxone	1.4 mg buprenorphine/ 0.36 mg naloxone	
	4 mg buprenorphine/ 1 mg naloxone		2.1 mg buprenorphine/ 0.3 mg naloxone
8 mg buprenorphine/ 2 mg naloxone	8 mg buprenorphine/ 2 mg naloxone	5.7 mg buprenorphine/ 1.4 mg naloxone	4.2 mg buprenorphine/ 0.7 mg naloxone
	12 mg buprenorphine/ 3 mg naloxone	8.6 mg buprenorphine/ 2.1 mg naloxone	6.3 mg buprenorphine/ 1 mg naloxone
		11.4 mg buprenorphine/ 2.9 mg naloxone	

Full Prescribing Information for all buprenorphine-containing products included in the BTOD REMS program can be found at www.btodrems.com.

II. REMS – RISK EVALUATION AND MITIGATION STRATEGY

What is a REMS?

A REMS is a strategy to manage a known or potential risk associated with a drug. A REMS can include, among other strategies, a Medication Guide, a communication plan, and elements to assure safe use.

Is there a REMS for buprenorphine-containing products?

Yes, a REMS has been implemented as part of the FDA requirements to ensure that the benefits of treatment with buprenorphine-containing products outweigh the potential risks, particularly risks of accidental overdose, misuse, and abuse.

The following products are covered under the Buprenorphine-containing Transmucosal products for Opioid Dependence (BTOD) REMS Program:

- Generic equivalents of Subutex® (buprenorphine hydrochloride) sublingual tablet
- Generic equivalents of Suboxone® (buprenorphine hydrochloride/naloxone hydrochloride) sublingual tablet
- Zubsolv® (buprenorphine/naloxone) sublingual tablet
- Bunavail™ (buprenorphine hydrochloride/naloxone hydrochloride) buccal film

The goals of the BTOD REMS are to:

- Mitigate the risks of accidental overdose, misuse, and abuse
- Inform prescribers, pharmacists, and patients of the serious risks associated with the use of buprenorphine-containing products

What is my role with regard to the BTOD REMS?

As part of the REMS, pharmacists dispensing buprenorphine-containing products for opioid dependence must supply a Medication Guide for the buprenorphine-containing product with each prescription. The Medication Guide will be provided with the product and is also available by going online to www.btodrems.com or calling 1-855-223-3922.

What is the role of the pharmacist in ensuring safe use of buprenorphine-containing products?

As a pharmacist, you will play an important role in ensuring that buprenorphine-containing products are used safely and appropriately. Each time you fill a prescription for a buprenorphine-containing product, make sure to:

- Verify that the prescription you receive is from a prescriber who is in compliance with the provisions of DATA 2000
- Keep in mind that a limited supply of buprenorphine-containing products should be dispensed during the initiation of therapy. This is due to the need of prescribers to closely and frequently assess the patients' needs, their symptoms, and potential risk of misuse, diversion, and abuse
- Provide the Medication Guide to patients each time the medicine is dispensed
- Remind patients who are picking up induction doses to return as directed to the doctor's office so that they can be supervised while taking the medication
- Explain how to safely store the medication out of reach of children
- Provide appropriate patient counseling on safe use of buprenorphine-containing products (see [Section VI. Patient Information](#))
- Be vigilant in detecting fraudulent prescriptions or simultaneous prescriptions for the same patient from multiple prescribers

III. HIGHLIGHTED IMPORTANT SAFETY INFORMATION FOR BUPRENORPHINE-CONTAINING PRODUCTS

This section of the brochure highlights important safety information to consider when prescribing or dispensing buprenorphine-containing products. **Please refer to the Full Prescribing Information (FPI) for detailed safety-related information for buprenorphine-containing products.**

Abuse Potential of Buprenorphine-Containing Products

Are buprenorphine-containing products abusable?

Yes, buprenorphine, like morphine and other opioids, has the potential for being abused and is subject to criminal diversion. This should be considered when dispensing buprenorphine in situations when there is a concern about an increased risk of misuse, abuse, or diversion. All healthcare professionals should contact their state professional licensing board or state controlled substances authority for information on how to prevent and detect abuse or diversion of this product.

Abuse of buprenorphine poses a risk of overdose and death. This risk is increased with the concomitant use of buprenorphine and alcohol and other substances, especially benzodiazepines.

Proper assessment of the patient, proper prescribing practices, periodic re-evaluation of therapy and proper handling and storage of the medication by the prescriber and patient are appropriate measures that help to limit abuse of opioid drugs.

Due to the partial agonist properties of buprenorphine, buprenorphine-containing products may precipitate opioid withdrawal signs and symptoms in persons dependent on full opioid agonists if administered before the agonist effects of the opioid have subsided. However, buprenorphine products that contain naloxone are highly likely to produce marked and intense withdrawal signs and symptoms if misused parenterally by individuals dependent on full opioid agonists such as heroin, morphine, or methadone. Therefore, to discourage misuse or abuse, it is highly recommended that, after induction, for unsupervised administration, buprenorphine with naloxone rather than buprenorphine alone is prescribed whenever feasible.

However, pharmacists should also be aware that some opioid-dependent persons can and do abuse buprenorphine/naloxone combinations by the intravenous or intranasal routes. This is especially true for opioid-dependent persons with a low level of full mu-opioid physical dependence or those whose opioid physical dependence is predominantly to buprenorphine.

Can buprenorphine-containing products cause dependence?

Yes, buprenorphine is a partial agonist at the mu-opioid receptor. Chronic administration produces dependence of the opioid type, characterized by withdrawal upon abrupt discontinuation or rapid taper. The withdrawal syndrome is milder than seen with full agonists, and may be delayed in onset. If cessation of therapy is indicated, it is appropriate to taper the buprenorphine dose, rather than abruptly discontinue the medication. The prescriber can provide a dose schedule to accomplish a gradual discontinuation of the medication.

Buprenorphine can be abused in a manner similar to other opioids, legal or illicit. This should be considered when prescribing or dispensing buprenorphine in situations where there is an increased concern about the possibility of misuse, diversion, or abuse.

How can patients prevent accidental exposure to buprenorphine-containing products in children?

Patients should be instructed to keep buprenorphine-containing products in a secure place, out of the sight and reach of children and other household members. Accidental or deliberate ingestion by a child may cause respiratory depression that can result in death. If a child is exposed accidentally to a buprenorphine-containing product, seek immediate urgent medical attention.

What is an appropriate medical response to an overdose on a buprenorphine-containing product?

In the case of overdose, the primary management should be the re-establishment of adequate ventilation with mechanical assistance of respiration, if required. Naloxone hydrochloride may be of value for the management of buprenorphine overdose. Higher than normal doses and repeated administration may be necessary.

Contraindications

- Hypersensitivity to buprenorphine and, in the case of combination products, naloxone

Warnings and Precautions

- Buprenorphine can be abused in a similar manner to other opioids. Clinical monitoring appropriate to the patient's level of stability is essential. Multiple refills should not be prescribed early in treatment or without appropriate patient follow-up visits
- Significant respiratory depression and death have occurred in association with buprenorphine, particularly when taken by the intravenous (IV) route in combination with benzodiazepines or other CNS depressants (including alcohol)
- Consider dose reduction of CNS depressants, buprenorphine-containing products, or both in situations of concomitant prescription
- Store buprenorphine-containing products safely out of the sight and reach of children. Buprenorphine can cause severe, possibly fatal, respiratory depression in children
- Chronic administration produces opioid-type physical dependence. Abrupt discontinuation or rapid dose taper may result in opioid withdrawal syndrome
- Monitor liver function tests prior to initiation and during treatment and evaluate suspected hepatic events
- Do not administer buprenorphine-containing products to patients with known hypersensitivity to buprenorphine or, in the case of combination products, naloxone
- An opioid withdrawal syndrome is likely to occur with parenteral misuse of buprenorphine-containing products by individuals physically dependent on full opioid agonists before the agonist effects of other opioids have subsided, particularly buprenorphine-containing products that also contain naloxone
- Neonatal withdrawal has been reported following use of buprenorphine by the mother during pregnancy
- Buprenorphine-containing products covered under the BTOD REMS are not appropriate as an analgesic. There have been reported deaths of opioid naive individuals who received a 2 mg sublingual dose
- Caution patients about the risk of driving or operating hazardous machinery
- For buprenorphine/naloxone combination products:
 - Not recommended in patients with **severe** hepatic impairment
 - Not recommended for initiation of treatment (induction) in patients with **moderate** hepatic impairment due to the increased risk of precipitated withdrawal. However, buprenorphine/naloxone products may be used with caution for maintenance treatment in patients with **moderate** hepatic impairment who have initiated treatment on a buprenorphine product without naloxone. However, patients should be carefully monitored and consideration given to the possibility of naloxone interfering with buprenorphine's efficacy.

- For buprenorphine sublingual tablets:
 - **Severe** hepatic impairment: Consider reducing the starting and titration incremental dose by half compared to patients with normal liver function, and monitor for signs and symptoms of toxicity or overdose caused by increased levels of buprenorphine.
 - **Moderate** hepatic impairment: Although no dose adjustment is necessary for patients with moderate hepatic impairment, buprenorphine sublingual tablets should be used with caution in these patients and prescribers should monitor patients for signs and symptoms of toxicity or overdose caused by increased levels of buprenorphine.

Adverse Reactions

What are the most commonly observed adverse events of buprenorphine-containing products?

- Adverse events most commonly observed with buprenorphine-containing products are: headache, nausea, vomiting, hyperhidrosis, constipation, signs and symptoms of withdrawal, insomnia, and pain. For a complete list of potential adverse events associated with buprenorphine-containing products, please see the Full Prescribing Information.
- To report SUSPECTED ADVERSE REACTIONS contact:
 - The manufacturer of the product taken or
 - FDA MedWatch program by phone at 1-800-FDA-1088 or online at www.fda.gov/medwatch/report.htm

Drug Interactions

- Monitor patients starting or ending CYP3A4 inhibitors or inducers for potential over or under dosing
- Use caution in prescribing buprenorphine-containing products for patients receiving benzodiazepines or other CNS depressants and warn patients against concomitant self-administration/misuse

Use in Specific Populations

- **Pregnancy:** Based on animal data, buprenorphine may cause fetal harm. Buprenorphine-containing products are not indicated for use during pregnancy unless potential benefit justifies potential risk
- **Nursing mothers:** Caution should be exercised when buprenorphine-containing products are administered to a nursing woman
- Safety and effectiveness of buprenorphine-containing products in patients below the age of 16 have not been established
- Administer buprenorphine-containing products with caution to elderly or debilitated patients
- Buprenorphine/naloxone products are not recommended for use in patients with severe hepatic impairment and may not be appropriate for patients with moderate hepatic impairment
- Buprenorphine sublingual tablets should be used with caution in patients with moderate to severe hepatic impairment and a dose adjustment is recommended for patients with severe hepatic impairment

IV. DISPENSING PRESCRIPTIONS FOR BUPRENORPHINE-CONTAINING PRODUCTS

This section discusses important information to consider before filling prescriptions for buprenorphine-containing products.

Who is qualified to prescribe buprenorphine-containing products?

A Federal law, Drug Addiction Treatment Act of 2000 (DATA 2000), limits office-based use of buprenorphine-containing products to prescribers who have met qualifications to receive a waiver.

How can I be sure a prescriber is qualified to prescribe buprenorphine-containing products?

Pharmacists can verify the validity of a prescriber's DATA 2000 waiver by calling 1-866-BUP-CSAT (1-866-287-2728), or e-mailing info@buprenorphine.samhsa.gov.

DEA regulations require that this number, along with the existing DEA registration number, is included on all prescriptions for buprenorphine-containing products for the treatment of opioid dependence.

What if I get a prescription from a doctor who does not have a special DEA identification number?

Call that prescriber for clarification and confirm that the prescriber has submitted a Notification of Intent form to SAMHSA. The DEA has developed regulations that require this number, along with the prescriber's existing DEA registration number, to be included on all prescriptions issued for the treatment of opioid dependence.

Most prescribers will make arrangements to obtain the identification number before prescribing buprenorphine-containing products, but in rare cases, a prescriber may need to write a prescription before the number has been issued. This is allowed under DATA 2000, provided the prescriber has notified SAMHSA of his/her intention to begin treating a patient immediately.

How can I verify that a prescription is legitimate?

According to federal law, pharmacists and prescribers jointly share legal responsibility for the legitimacy of a prescription. Communication between you and the prescriber is vital to ensure the validity of each prescription you're asked to fill.

However, even if you determine that an individual prescription is legitimate, you should still be aware of other means by which patients may attempt to divert their prescriptions. For example, an opioid user may present themselves to 2 or more qualified prescribers and therefore, receive multiple prescriptions for buprenorphine-containing products. If a patient brings you more than 1 prescription covering the same therapeutic period, you have a legal duty to recognize that they may not be for therapeutic use. You should contact each prescriber for verification and notify them of the additional pending prescription.

What should I do if I am seeing prescriptions from a single prescriber that seem to exceed the patient limit?

Prescribers agree to treat no more than 30 patients at a time during the first year of providing buprenorphine treatment. After a year, their patient limit may be increased to 100 patients.

If you are concerned about the validity of the prescription for any reason, including exceeding the patient limit, begin by contacting

the prescriber for clarification. In some cases, the prescriber needs the patient's consent to discuss specific patient issues.

You can also contact: SAMHSA/CSAT at 1-866-BUP-CSAT (1-866-287-2728) or by email: info@buprenorphine.samhsa.gov; DEA (www.deadiversion.usdoj.gov); and the State Board of Medicine (a list of contact numbers may be found at this website: www.fsmb.org/directory_smb.html).

Are there confidentiality issues I should be aware of related to substance abuse treatment?

People with opioid dependence are more likely to seek and continue with treatment when they know their treatment will be held in strict confidence.

For this reason, federal regulations protect the privacy of patients' medical information, namely Title 42 Part 2 of the Code of Federal Regulations (42 CFR Part 2) and the Health Insurance Portability and Accountability Act (HIPAA).

42 CFR Part 2 states that any patient-identifying information pertaining to treatment for substance abuse must be handled with a greater degree of confidentiality than patients' general medical information.

Under 42 CFR Part 2, before a prescriber can disclose any information to a third party about a patient's treatment for substance abuse, that prescriber must first obtain the patient's signed consent.

When a prescriber directly transmits a prescription for a buprenorphine-containing product to your pharmacy, any redisclosure of that patient-identifying information by the pharmacy is prohibited without the patient's signed consent.

According to 42 CFR Part 2, the following elements are required for a consent form to be considered valid:

- Patient's name, prescriber's name, pharmacist's name
- Purpose of the disclosure; recipient of the disclosure
- What information will be released
- An indication that the patient understands he/she can revoke this consent at any time and that this revocation can be verbal
- The date and terms under which the consent expires
- Patient's dated signature

To learn more about these regulations, visit the SAMHSA website, <http://www.samhsa.gov/healthprivacy/>, or call 1-866-BUP-CSAT (1-866-287-2728).

Are there any special storage, record keeping, or other requirements associated with buprenorphine-containing products?

Buprenorphine-containing products are Schedule III controlled substances; therefore, buprenorphine-containing products are subject to certain federal regulations covering areas such as record keeping, inventory, proper dispensing and disposal. These are explained in the DEA's Pharmacist's Manual, which can be found at www.deadiversion.usdoj.gov/pubs/manuals/pharm2/index.html. Many states have their own additional requirements for pharmacists dispensing controlled substances. Be sure to check with the appropriate authority in your state. For more information, visit the website of the National Association of Boards of Pharmacy at www.nabp.net for links to individual state boards of pharmacy.

V. SUPPLYING AND ADMINISTERING BUPRENORPHINE-CONTAINING PRODUCTS

How are buprenorphine-containing products supplied?

Subutex (Buprenorphine sublingual tablets), including generic equivalents:	2 mg buprenorphine 8 mg buprenorphine
Suboxone (Buprenorphine and naloxone sublingual tablets), including generic equivalents:	2 mg buprenorphine / 0.5 mg naloxone 8 mg buprenorphine / 2 mg naloxone
Zubsolv (Buprenorphine and naloxone sublingual tablets):	1.4 mg buprenorphine / 0.36 mg naloxone 5.7 mg buprenorphine / 1.4 mg naloxone 8.6 mg buprenorphine / 2.1 mg naloxone 11.4 mg buprenorphine / 2.9 mg naloxone
Suboxone sublingual film (Buprenorphine and naloxone sublingual film):	2 mg buprenorphine / 0.5 mg naloxone 4 mg buprenorphine / 1 mg naloxone 8 mg buprenorphine / 2 mg naloxone 12 mg buprenorphine / 3 mg naloxone
Bunavail (Buprenorphine hydrochloride and naloxone hydrochloride buccal film):	2.1 mg buprenorphine / 0.3 mg naloxone 4.2 mg buprenorphine / 0.7 mg naloxone 6.3 mg buprenorphine / 1 mg naloxone

How should buprenorphine with or without naloxone be administered?

For buprenorphine-containing tablets, the patient should place tablets under the tongue until they are dissolved. For doses requiring the use of more than 2 tablets, patients are advised to either place all the tablets at once or alternatively (if they cannot fit in more than 2 tablets comfortably), place 2 tablets at a time under the tongue. Either way, the patients should continue to hold the tablets under the tongue until they dissolve; swallowing the tablets reduces the bioavailability of the drug. To ensure consistency in bioavailability, patients should follow the same manner of dosing with continued use of the product.

For Bunavail buccal film administration, the patient should use the tongue to wet the inside of the cheek or rinse the mouth with water to moisten the area immediately before placement of Bunavail; open the Bunavail package immediately prior to use as indicated by the instructions; place the Bunavail film near the tip of a dry finger with the text facing up; place the side of the Bunavail film with the text against the inside of the cheek; press and hold the film in place for 5 seconds. Bunavail film(s) adhere to the moist buccal mucosa and should stay in place after this period.

If multiple films need to be administered, the patient should immediately apply the next film. Note that when two films are required for one dose, the patient should place one film on the inside of each cheek. For doses requiring multiple films, no more than two films should be applied to the inside of one cheek at a time. The patient should be instructed to avoid manipulating the film(s) with their tongue or finger(s) and avoid drinking or eating food until the film(s) dissolve.

For Suboxone sublingual film, the patient should place the Suboxone film under the tongue. If an additional film is necessary to achieve the prescribed dose, the additional film should be placed sublingually on the opposite side from the first film. If an additional third film is needed, place it sublingually after the first 2 Suboxone sublingual films have dissolved. Place Suboxone sublingual films in a manner to minimize overlapping as much as possible. Keep the films under the tongue, close to the base on the left or right side, until

they are completely dissolved. Suboxone sublingual film should NOT be chewed, swallowed, or moved after placement.

VI. PATIENT INFORMATION

What information about the safe use of buprenorphine-containing products needs to be communicated to patients?

The safety concerns related to the use of buprenorphine-containing products includes, but are not limited to, the following:

- Warn patients that it is extremely dangerous to self-administer non-prescribed benzodiazepines or other CNS depressants (including alcohol) while taking buprenorphine-containing products. Patients prescribed benzodiazepines or other CNS depressants should be cautioned to use them only as directed by their prescriber
- Instruct patients to keep buprenorphine-containing products in a secure place, out of the sight and reach of children. Accidental or deliberate ingestion by a child may cause respiratory depression that can result in death. Patients should be advised that if a child is exposed to buprenorphine-containing products, medical attention should be sought immediately
- Advise patients that buprenorphine-containing products contain an opioid that can be a target for people who abuse prescription medications or street drugs. Patients should be cautioned to keep their products in a safe place and to protect them from theft
- Instruct patients never to give buprenorphine-containing products to anyone else, even if he or she has the same signs and symptoms. It may cause harm or death
- Advise patients that selling or giving away buprenorphine-containing products is against the law
- Caution patients that buprenorphine-containing products may impair the mental or physical abilities required for the performance of potentially dangerous tasks, such as driving or operating machinery. Caution should be taken, especially during drug induction and dose adjustments and until they are reasonably certain that buprenorphine-containing products do not adversely affect their ability to engage in such activities
- Advise patients not to change the dose of buprenorphine-containing products without consulting their prescriber
- Advise patients to take buprenorphine-containing products once a day as directed
- Inform patients that buprenorphine-containing products can cause drug dependence of the opioid type. Withdrawal signs and symptoms may occur when the medication is discontinued
- Advise patients seeking to discontinue treatment with buprenorphine-containing products for opioid dependence to work closely with their prescriber on a tapering schedule, and apprise of the potential to relapse to illicit drug use associated with discontinuation of opioid agonist/partial agonist medication-assisted treatment
- Caution patients that, like other opioids, buprenorphine-containing products may produce orthostatic hypotension in ambulatory individuals
- Ask patients if other prescription medications, over-the-

counter medications or herbal preparations are prescribed or are currently being used

- Advise patients who become pregnant, or are planning to become pregnant, to consult their prescriber regarding the possible effects secondary to using buprenorphine-containing products during pregnancy
- Buprenorphine and naloxone-containing products should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.
- Based on two studies in 13 lactating women, buprenorphine and its metabolite norbuprenorphine are present in low levels in human milk and infant urine, and available data have not shown adverse reactions in breastfed infants. There are no data on the combination product buprenorphine/naloxone in breastfeeding; however oral absorption of naloxone is minimal. Caution should be exercised when buprenorphine-containing products are administered to a nursing woman. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for buprenorphine-containing products and any potential adverse effects on the breastfed child from the drug or from the underlying maternal condition.
- Advise the nursing mother taking buprenorphine and naloxone-containing products to monitor the infant for increased drowsiness and breathing difficulties.
- Ask patients to inform their family members or other appropriate individuals that, in the event of emergency, the treating prescriber or emergency department staff should be informed that the patient is physically dependent on an opioid and that the patient is being treated with buprenorphine-containing products
- Instruct patients to dispose of unused buprenorphine-containing products as soon as it is no longer needed. Unused tablets and films (after they have been removed from the foil package) should be flushed down the toilet.

VII. WHERE CAN I GET MORE INFORMATION ON TREATING OPIOID ADDICTION WITH BUPRENORPHINE-CONTAINING PRODUCTS?

Refer to the package insert of the product you are dispensing for full information on the adverse reactions seen during the clinical trials using buprenorphine for opioid dependence treatment

General information about buprenorphine treatment and the treatment of addiction are available through numerous sources, including but not limited to:

- SAMHSA website (www.dpt.samhsa.gov)
- American Society of Addiction Medicine website (www.asam.org)
- American Academy of Addiction Psychiatry website (www.aaap.org)

For more information:

www.btodrems.com

BTOD REMS call center (toll-free)
1-855-223-3922



Buprenorphine-containing Transmucosal products for
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The Food and Drug Administration (FDA) has required a Risk Evaluation and Mitigation Strategy (REMS) for Buprenorphine-containing Transmucosal products for Opioid Dependence (BTOD)

A REMS is a strategy to manage known or potential serious risks associated with a drug product and is required by the FDA to ensure that the benefits of a drug outweigh its risks.

The purpose of the BTOD REMS program is to inform healthcare professionals and patients about the safe use conditions and serious risks, including accidental overdose, misuse, and abuse, associated with buprenorphine-containing transmucosal products indicated for the treatment of opioid dependence.

Prescribers should:

- **Verify** that patients meet diagnostic criteria for opioid dependence
- **Counsel** patients and/or their caregivers on safe use of the product, including appropriate storage and disposal, and risks associated with treatment, at each visit
- **Monitor and document** safe use conditions for each patient by using the [Appropriate Use Checklist](#) (or by other means specific to office practice)
- **Assess** appropriateness of treatment and adequate progress towards treatment goals for each patient

To prescribe products covered under the BTOD REMS, a prescriber must be certified to treat opioid dependence under the Drug Addiction Treatment Act of 2000 (DATA 2000). For certification information, [click here](#).

[Click here for a complete list of products covered under the BTOD REMS program](#)

Materials for Prescribers:

[Dear Prescriber Letter](#)

[Office-Based Buprenorphine Therapy for Opioid Dependence: Important Information for Prescribers](#)

[Appropriate Use Checklist](#)

Materials for Pharmacists:

[Dear Pharmacist Letter](#)

[Office-Based Buprenorphine Therapy for Opioid Dependence: Important Information for Pharmacists](#)

Materials for Patients:

[Medication Guides](#)

For more information or to receive print copies of the materials, please call: **1-855-223-3922**.

This REMS does not apply to buprenorphine containing products indicated for the treatment of pain or for products dispensed to patients admitted to Opioid Treatment Programs (OTP) under 42 CFR part 8.

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Important Safety Information

The drug products subject to the Buprenorphine containing Transmucosal products for Opioid Dependence (BTOD) REMS¹ include:

- Generic equivalents of Subutex® (buprenorphine hydrochloride) sublingual tablet
- Generic equivalents of Suboxone® (buprenorphine hydrochloride/naloxone hydrochloride) sublingual tablet
- Zubsolv® (buprenorphine/naloxone) sublingual tablet
- Bunavail™ (buprenorphine hydrochloride/naloxone hydrochloride) buccal film

¹Buprenorphine hydrochloride sublingual tablets marketed under the trade name Subutex® and buprenorphine hydrochloride/naloxone hydrochloride sublingual tablets and sublingual film marketed under the trade name Suboxone® are covered under the Subutex and Suboxone REMS programs.

These products, collectively referred to as "buprenorphine containing products", are delivered by the oral transmucosal route and are indicated for use during treatment of opioid dependence as part of a comprehensive treatment plan to include counseling and psychosocial support. Treatment must be initiated under the direction of prescribers qualified under the Drug Addiction Treatment Act of 2000.

Buprenorphine containing products must not be used by patients with hypersensitivity to buprenorphine, and/or naloxone in the case of combination products.

Buprenorphine containing products can be abused in a manner similar to other opioids, legal or illicit. Clinical monitoring appropriate to the patient's level of stability is essential.

Children who ingest buprenorphine containing products can have severe, possibly fatal, respiratory depression. Emergency medical care is critical. Keep buprenorphine containing products out of the sight and reach of children.

Buprenorphine containing products can cause serious life threatening respiratory depression and death, particularly when taken by the intravenous (IV) route in combination with benzodiazepines or other central nervous system (CNS) depressants (i.e., sedatives, tranquilizers, or alcohol). It is extremely dangerous to self administer nonprescribed benzodiazepines or other CNS depressants while taking buprenorphine containing products. When buprenorphine containing products are taken together with CNS depressants, dose reduction of either product(s) should be considered.

Death has been reported in nontolerant, nondependent individuals who received a 2 mg dose for analgesia. The products covered under this REMS are not appropriate for use as an analgesic.

Chronic use of buprenorphine can cause physical dependence. A sudden or rapid decrease in dose may result in an opioid withdrawal syndrome that is typically milder than seen with full agonists (e.g., heroin, hydrocodone, methadone, morphine, oxycodone) and may be delayed in onset. Intravenous misuse or taking buprenorphine containing products before the effects of full agonist opioids have subsided is highly likely to cause opioid withdrawal symptoms.

Liver function should be monitored before and during treatment.

Use of buprenorphine containing products in pregnant women or during breast feeding should only be considered if the potential benefit justifies the potential risk. Neonatal withdrawal has been reported.

Caution should be exercised when driving vehicles or operating hazardous machinery, especially during dose adjustment.

Adverse events most commonly observed with the sublingual administration of buprenorphine during clinical trials and post marketing experience are headache, nausea, vomiting, hyperhidrosis, constipation, signs and symptoms of withdrawal, insomnia, and pain. An additional adverse event among those most commonly observed with sublingual administration of buprenorphine/naloxone formulations is peripheral edema.

Cytolytic hepatitis, jaundice, and allergic reactions, including anaphylactic shock, have been reported. Adverse events most commonly observed with the buccal administration of the buprenorphine/naloxone formulation were signs and symptoms of withdrawal and headache.

This is not a complete list of potential adverse events associated with buprenorphine containing products. Please see [Full Prescribing Information](#) of each specific product for a complete list.

For more information about the BTOD REMS, including all program materials and instructions call **1-855-223-3922**.

To report SUSPECTED ADVERSE EVENTS, contact:

- The manufacturer of the product taken or
- FDA MedWatch program by phone at 1 800 FDA 1088 or online at www.fda.gov/medwatch/report.htm

Please see [Full Prescribing Information](#) and [Medication Guide](#) for all buprenorphine-containing products.

Materials for Prescribers:

[Dear Prescriber Letter](#)

[Office Based Buprenorphine Therapy for Opioid Dependence: Important Information for Prescribers](#)

[Appropriate Use Checklist](#)

Materials for Pharmacists:

[Dear Pharmacist Letter](#)

[Office Based Buprenorphine Therapy for Opioid Dependence: Important Information for Pharmacists](#)

Materials for Patients:

[Medication Guides](#)

For more information or to receive print copies of the materials, please call: **1-855-223-3922**.



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Trade Name	Company	Phone Number	Information Links

Buprenorphine/Naloxone Combination Ingredient Products

Trade Name	Company	Phone Number	Information Links

**Materials for
Prescribers:**[Dear Prescriber Letter](#)[Office Based Buprenorphine Therapy
for Opioid Dependence: Important
Information for Prescribers](#)[Appropriate Use Checklist](#)**Materials for Pharmacists:**[Dear Pharmacist Letter](#)[Office Based Buprenorphine Therapy
for Opioid Dependence: Important
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For more information or to receive
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call: **1 855 223 3922**.

The BPMG attests that the table above will only include products listed in the link titled 'List of approved application numbers and sponsors' on the FDA Approved
REMS website.

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Getting Certified

Under the Drug Addiction Treatment Act of 2000 (DATA 2000), prescription use of buprenorphine-containing products in the treatment of opioid dependence is limited to prescribers who meet certain qualifying requirements, and who have notified the Secretary of Health and Human Services (HHS) of their intent to prescribe this product for the treatment of opioid dependence and have been assigned a unique identification number that must be included on every prescription.

To become certified to prescribe buprenorphine-containing products, you will need to follow certification guidelines set by DATA 2000.

Detailed information about DATA 2000, qualifications, notifying SAMHSA, and the general prescriber waiver process can be found at buprenorphine.samhsa.gov, or by contacting SAMHSA directly:

SAMHSA Buprenorphine Information Center

Phone: 1-866-287-2729 (866-BUP-CSAT)

E-mail: info@buprenorphine.samhsa.gov

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/s/

JUDITH A RACOOSIN
02/12/2015